

Revista da
ASSOCIAÇÃO MÉDICA BRASILEIRAwww.ramb.org.br**Original article****Heparin-induced thrombocytopenia: a review of concepts regarding a dangerous adverse drug reaction[☆]****Daniela Rezende Garcia Junqueira^{a,b,*}, Maria das Graças Carvalho^b, Edson Perini^b**^a The University of Sydney, Sydney, Australia^b Centro de Estudos do Medicamento (Cemed), Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil**A R T I C L E I N F O****Article history:**

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A B S T R A C T

Heparin is a natural agent with antithrombotic action, commercially available for therapeutic use as unfractionated heparin and low molecular weight heparin. Heparin-induced thrombocytopenia (HIT) is a serious adverse reaction to heparin that promotes antibody-mediated platelet activation. HIT is defined as a relative reduction in platelet count of 50% (even when the platelet count at its lowest level is above $> 150 \times 10^9/L$) occurring within five to 14 days after initiation of the therapy. Thrombocytopenia is the main feature that directs the clinical suspicion of the reaction and the increased risk of thromboembolic complications is the most important and paradoxical consequence. The diagnosis is a delicate issue, and requires a combination of clinical probability and laboratory tests for the detection of platelet activation induced by HIT antibodies. The absolute risk of HIT has been estimated between 1% and 5% under treatment with unfractionated heparin, and less than 1% with low molecular weight heparin. However, high-quality evidence about the risk of HIT from randomized clinical trials is scarce. In addition, information on the frequency of HIT in developing countries is not widely available. This review aims to provide a better understanding of the key features of this reaction and updated information on its frequency to health professionals and other interested parties. Knowledge, familiarity, and access to therapeutic options for the treatment of this adverse reaction are mandatory to minimize the associated risks, improving patient safety.

© 2013 Elsevier Editora Ltda. Este é um artigo Open Access sob a licença de [CC BY-NC-ND](http://creativecommons.org/licenses/by-nc-nd/4.0/)**Trombocitopenia induzida por heparina: revisão de conceitos de uma importante reação adversa a medicamentos****R E S U M O**

A heparina é um agente natural com ação antitrombótica, sendo disponibilizadas para uso terapêutico a heparina não fracionada e a heparina de baixo peso molecular. A trombocitopenia induzida por heparina (TIH) é uma reação adversa grave às heparinas mediada por anticorpos que promovem ativação de plaquetas. A TIH é definida como uma redução relativa na contagem de plaquetas de 50% (mesmo se a contagem de plaquetas no seu nível mais

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baixo estiver acima $150 \times 10^9/L$) que pode ocorrer no período de cinco a 14 dias após o início da terapia com o medicamento. A trombocitopenia é a principal característica que direciona a suspeita clínica da reação, sendo o aumento do risco de complicações tromboembólicas a consequência mais importante e paradoxal. O diagnóstico é uma questão delicada e requer a combinação da probabilidade clínica com testes laboratoriais para detectar a ativação plaquetária induzida pelos anticorpos da TIH. O risco absoluto de TIH tem sido estimado entre 1 e 5% no tratamento com heparina não fracionada e inferior a 1% no uso de heparina de baixo peso molecular. No entanto, evidências de alta qualidade provenientes de ensaios clínicos randomizados sobre a frequência dessa reação são escassas. Além disso, informações sobre a frequência de TIH em países em desenvolvimento não são amplamente disponíveis. Esta revisão teve como objetivo fornecer aos profissionais de saúde e demais interessados um melhor conhecimento sobre a TIH e as principais características dessa reação, bem como apresentar dados atualizados sobre a frequência da mesma. Conhecimento, familiaridade e acesso a opções terapêuticas para o tratamento dessa reação adversa são necessários para minimizar os riscos associados, melhorando a segurança do paciente.

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Introduction

Heparin is one of the most commonly used medications worldwide, with over one trillion units used in the United States yearly.¹ It is an anticoagulant that occurs naturally in the organism in small amounts, and whose activity is expressed through ligation to a plasma cofactor, the antithrombin, thus inactivating thrombin (factor IIa) and factors Xa, IXa, and Xla.² For medicinal purposes, the drug is extracted from animal mucosa (swine or bovine), and used mainly in the treatment and prophylaxis of thromboembolic disorders.

There are two types of heparin drugs available: unfractionated heparin (UFH), also called standard heparin; and low-molecular-weight heparin (LMWH). UFH is a heterogeneous mixture of glycosaminoglycans with molecular weight ranging from 3,000 to 30,000 on average. LMWH is obtained by fractionation or depolymerization of standard heparin yielding fragments, with mean molecular weight ranging from 4,500 to 5,000.^{2,3} Therefore, LMWH constitutes a group of several drugs (e.g. enoxaparin, dalteparin, nadroparin, tinzaparin, etc.) differing in some extent in their pharmacokinetic properties and anticoagulant profile, since they are prepared by different methods of depolymerization. LMWH presents a more predictable dose-response relationship and an improved bioavailability after subcutaneous administration due to reduced binding to plasma proteins, macrophages, and endothelial cells, thus allowing for a fixed-dose regime.^{2,4}

Among the possible adverse effects during treatment with heparin, hemorrhage is the main and best-known risk, occurring in 5% to 10% of exposed patients.³ Another important adverse drug reaction faced by clinicians during treatment with heparin is heparin-induced thrombocytopenia (HIT), potentially the most morbid complication of heparin therapy. Formerly termed white clot syndrome or HIT type II, HIT is a type of acquired hypercoagulability syndrome caused by an immune-mediated reaction induced by the heparin compound, and commonly followed by venous or arterial thrombosis.⁵⁻⁷ The first report of the association of HIT with thrombosis dates from 1958; since then, there has been a massive effort to explain this intriguing syndrome.

Purpose of the review

Considering the potential consequences of a thrombotic event, HIT is an important and life-threatening adverse drug reaction following treatment with heparin. Therefore, this study aimed to review the literature addressing key characteristics of this syndrome, its frequency, and diagnostic issues, in order to aid HIT recognition in daily clinical practice.

Pathophysiology of heparin-induced thrombocytopenia

The pathophysiology of the thrombocytopenia in HIT is still not completely understood.⁸ According to the elucidated mechanism, following the administration of heparin, platelet factor 4 (PF4), a small peptide stored in platelet α -granules, is released in blood circulation due to a transient and unspecific platelet aggregation induced by direct interaction of platelets with heparin.⁹ Subsequently, heparin binds to PF4 due to charge differences, thus resulting in a macromolecular complex (PF4/heparin). The formation of this complex induces a conformational change in the molecules, resulting in the formation of several neo-epitopes.^{2,10,11} An immune response against these antigenic epitopes results in the production of IgG, IgM, and IgA antibodies.

The clinical importance of IgA and IgM antibodies remains uncertain, as they appear unable to cause platelet activation in the presence of heparin,^{12,13} although in a few HIT cases (<10%), only IgA or IgM antibodies to PF4/heparin are detectable.¹¹ The IgG antibodies react with the PF4/heparin complex, forming an immunocomplex of PF4/heparin/IgG antibodies (HIT antibodies), which has the ability to bind to platelets' surfaces through their Fc γ RIIa receptor, inducing platelet activation and aggregation.^{14,15} The intensive platelet activation induced by HIT antibodies increases thrombin generation, thus determining a hypercoagulability state.^{16,17}

Observational data regarding the prevalence of HIT in the setting of local or systemic inflammation have also raised the possibility that additional cell types are involved in the pathogenesis of thrombosis, including leukocyte-platelet

aggregates and monocytes.^{8,18} HIT antibodies can bind to monocytes, prompting their degranulation and the release of several procoagulant and inflammatory substances.¹⁹ Moreover, there is evidence that activated monocytes express tissue factor on their surface, which reinforces the activation of the coagulation pathway.⁶ The activated coagulation system also determines the release of vesicular platelet-membrane (platelet microparticles), which contains substances (GPIb, GPIIb, and GPIIIa, P-selectin, and thrombospondin) capable of increasing thrombin generation *in vivo*.^{10,20,21} In addition, endothelial damage certainly plays a role in HIT pathogenesis, since it can be caused by immunoglobulins, cytokines released by activated leukocytes, microparticles from activated platelets, adhesion molecules from both activated platelets and leukocytes, as well as by mechanical disruption due to surgical processes or pathological processes such as atherosclerosis.⁶ Recently, in the setting of cardiothoracic patients, one study reported that HIT patients have positive antibodies to Adamts-13 and a reduced concentration of Adamts-13, which could be a complicating factor in HIT pathogenesis.²² Considering that patients needing antithrombotic therapy with heparin may be bedridden at least to some extent, the procoagulant state, together with vascular injury and stasis, may be a central mechanism of the venous and arterial thrombosis associated with the development of HIT.

It has been shown that there is dissociation between the development of HIT antibodies and the risk of HIT occurrence.²³ Therefore, not all patients who form HIT antibodies will develop thrombocytopenia or other sequelae of HIT.^{7,24} The reticuloendothelial system may clear platelets coated with antibodies from circulation, thus preventing the clinical manifestation of HIT in most patients.¹⁹ However, the reason why some patients develop antibodies with the ability to activate platelets (functional antibodies) and others do not is currently unknown.²⁵

Definitions and fundamental characteristics of heparin-induced thrombocytopenia

HIT is defined as a relative reduction in platelet count of 50% (even when the count of platelets at its lowest level is above $>150 \times 10^9/L$) occurring within five to 14 days after starting heparin therapy.²⁶ Remarkably, HIT differs from a non-immune heparin-associated thrombocytopenia (HAT), which is secondary to a direct interaction of heparin with platelets and resolves spontaneously.¹⁰

The time pattern of HIT may be difficult to recognize in the postoperative setting since platelet counts commonly decrease after a surgical procedure.²⁶ Therefore, in postoperative patients, thrombocytopenia in HIT may be defined as a drop in platelet counts of 50% or more from the maximum number of platelets, occurring after surgery and within the predefined time frame.²⁷ Noticeably, patients recently exposed to heparin may have circulating antibodies, and then they can develop rapid-onset HIT within 24 hours after a new heparin administration.¹³ Delayed-onset HIT, when the syndrome occurs months after the discontinuation of heparin, has also been described.^{28,29} Delayed-onset HIT is typically recognised because of a thrombotic event; the possibility of an

unsuccessful long-term anticoagulant therapy is a challenge to the diagnosis of the syndrome.¹²

Clinical suspicion of this adverse drug reaction mainly occurs because of thrombocytopenia, which is the central feature of the syndrome. However, the clinical suspicion must be confirmed by the demonstration of antibodies with ability to induce platelet activation.²⁶ Thrombotic events may also prompt a suspicion of HIT, since these complications can occur in an unpredictable manner throughout the use of the drug, and even before thrombocytopenia status is reached.^{7,30}

Diagnosis and treatment of heparin-induced thrombocytopenia

The diagnosis of HIT is a challenging issue. It requires the combination of clinical likelihood and laboratory tests to detect platelet activation induced by HIT antibodies.^{31,32} Some assays, known as functional assays, are able to demonstrate the presence of clinically relevant antibodies.³³ These assays are the C-serotonin released assay (SRA)¹⁴ and the heparin-induced platelet activation assay (HIPA), which also present the most favourable sensitivity/specificity trade-off.^{33,34}

The platelet aggregation assay has also been used, but lacks adequate sensitivity and is not generally recommended.³⁵ Another available procedure is detection of HIT antibodies in the patient's sera through immunoassays. There are a number of commercial enzyme-linked immunoassays (ELISA) available to diagnose HIT. They are able to detect pathogenic and non-pathogenic antibodies, and commonly lead to a high rate of false-positives.³³ However, despite their low specificity, these assays represent an ideal test to rule out HIT; their combination with a functional assay can be a valuable procedure to screen negative cases. Thus, functional assays should be reserved to just a small numbers of cases.

A clinical scoring system aiming to improve the clinical diagnosis of HIT has been developed.³² Using four clinical features of HIT (magnitude of thrombocytopenia, timing of thrombocytopenia regarding heparin exposure, occurrence of thrombosis or other sequelae, and absence of other explanations for the thrombocytopenia), the 4Ts scoring system is a risk assessment tool that classifies patients within low, moderate, and high probabilities for HIT. Several studies have investigated the usefulness of combining the 4Ts scoring system and laboratory testing in the diagnosis of HIT.^{36,37} However, this method may lack satisfactory ability to identify the probability of HIT in order to be widely used in clinical practice.^{38,39}

Considering the role of thrombin generation in HIT pathogenesis, all sources of heparin should be suspended when the reaction occurs. In case of a strong suspicion, the results of the assays should not even be waited for.⁴⁰ However, the cost-benefit of introducing a treatment with an alternative anticoagulant must be considered in the clinical decision-process, due to significant risk of bleeding.³⁴ There is a rationale for the use of direct thrombin inhibitors (argatroban, lepirudin, or bivalirudin) and of an agent anti-factor Xa (fondaparinux) that inhibits thrombin generation to treat HIT. Treatment must continue until platelet count becomes normal, and asymptomatic thrombosis should be investigated.

In cases of HIT complicated by thromboembolic events, therapy with alternative anticoagulants must be carefully followed by therapy with warfarin for two or three months.³⁵ An evidence-based guideline regarding the management of HIT is available.¹⁹

Some procedures should be avoided in the management of HIT. LMWH is not a therapeutic option, since it cross-reacts with circulating HIT antibodies.^{31,40} Oral anticoagulant drugs must also not be used because they reduce protein C and S levels, thus contributing to an increase in thrombin generation and resulting in a higher risk of thromboembolic complications.³² Indeed, venous gangrene has developed in patients treated for HIT with oral anticoagulants. Therefore, warfarin therapy may be carefully started only after the platelet count becomes normal. Platelet transfusion should not be performed, as it might induce or exacerbate thromboembolic complications.⁴⁰

Frequency of heparin-induced thrombocytopenia

HIT may develop following any mode of heparin administration,^{10,34} including parenteral infusions,²⁸ subcutaneous therapy,⁴¹ and even due to low-grade exposures such as heparin line flushes or following the insertion of heparin-bonded pulmonary artery catheters.⁴² The development of HIT is influenced by the type of heparin used (UFH or LMWH) and the type of heparin-exposed patient population.³⁴ Also, the incidence of HIT appears to be higher with the use of bovine heparin when compared with swine heparin. However, data regarding accurate values of the incidence of HIT are conflicting.³⁴ Overall, it has been generally accepted that the absolute risk of HIT during treatment with UFH is between 1% to 5%, and between 0.1% to 1% with LMWH.^{19,26,43} The association of HIT with the type of heparin may be justified by the higher molecular weight and degree of sulphation of the UFH, which determine a higher probability to induce the formation of HIT antibodies when compared to the LMWH.

The highest risk population comprises postoperative patients receiving UFH (estimated incidence between 1% to 5%).³⁴ Postoperative patients receiving LMWH show a lower risk of HIT (estimated incidence between 0.1% to 1%), together with medical and obstetrical patients exposed to UFH.⁴¹ In other settings, such as medical and obstetrical patients exposed only to LMWH or receiving catheter flushes with UFH, HIT is described as a rare event, with an incidence <0.1%,³⁴ although higher frequencies have been observed.⁴⁴ Specific characteristics of patients submitted to certain surgeries were also shown to influence the risk profile of HIT;^{18,23} however, most studies have enrolled patients after orthopedic surgery.

Recent investigations presented weak evidence supporting the generally accepted incidence of HIT. Although a lower incidence of HIT in postoperative patients under thromboprophylaxis with LMWH when compared with UFH was shown, randomized clinical trials that include HIT as an outcome are scarce.⁴⁵ Of note, in a recently published systematic review, the absolute risk (incidence) of HIT in patients subjected to major surgeries was found to be similar for both types of heparins (incidence >1% and <10%).⁴⁵ These

findings are preliminary, but may possibly impact clinical recommendations regarding platelet count monitoring during thromboprophylaxis with heparin.

Special concern should be addressed regarding the frequency of HIT in Brazil. To the authors' knowledge, there is no available information about the incidence of HIT in Brazil or in Latin America, and little information is available about the frequency of HIT in other developing countries. This is a concern, since the specificities in the population composition and its genetics can clearly influence the effects of drugs.⁴⁶ Most importantly, bovine heparin has shown a higher potential to induce HIT when compared with swine heparin. While most countries do not produce this kind of heparin anymore, 40% of the manufactured products containing heparin in Brazil are derived from a bovine source.⁴⁷ Therefore, there is a need for an improvement of knowledge and awareness regarding the occurrence of this adverse drug reaction in the clinical practice of Brazil. The poorly understood picture of HIT in this country may contribute to a delayed recognition of the syndrome, thus negatively impacting morbidity and mortality of patients.

Conflict of interest

All authors declare to have no conflict of interest.

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